

Health Technology Briefing

December 2024

Deutetrabenazine for treating tardive dyskinesia

Company/Developer

Teva Pharmaceuticals Ltd

☒ New Active Substance

☐ Significant Licence Extension (SLE)

NIHRIO ID: 31411

NICE ID: Not available

UKPS ID: 675006

Licensing and Market Availability Plans

Completed phase III clinical development.

Summary

Tardive dyskinesia is a chronic disorder characterised by involuntary stereotyped, choreic (jerky and unpredictable), athetoid (slow and writhing), and/or dystonic (sustained or repetitive) movements in one or more areas of the body, including the orofacial region (e.g., tongue thrusting, lip smacking and/or pursing, grimacing), extremities (e.g., stereotypic piano-playing movements, flexion/extension of the ankles or toes), and torso (e.g., pelvic rocking). It is a late (tardive) complication commonly associated with long-term use of certain medications, particularly antipsychotics. The reasons that some people who take these medicines may get tardive dyskinesia, and some people do not, is unknown. For patients suffering from tardive dyskinesia, these uncontrolled movements can be disruptive and disabling, significantly impacting their quality of life. There are limited treatment options available for the management of tardive dyskinesia, and no clear standard of care.

Deutetrabenazine, is a type of medication that blocks the action of a protein called vesicular monoamine transporter (VMAT2) which controls the levels of dopamine (type of chemical messenger) in the brain. By blocking VMAT2, deutetrabenazine reduces the levels of dopamine in the brain which results in a decrease in jerk-like movements. If licensed, deutetrabenazine which is administered orally, will offer a new treatment option for tardive dyskinesia.

Proposed Indication

For the treatment of tardive dyskinesia in patients aged 18 years and older.¹

Technology

Description

Deutetrabenazine (Austedo) is a selective reversible inhibitor of vesicular monoamine 2 transporter (VMAT2), that is designed to regulate the levels of the neurotransmitter dopamine, in the brain.^{2,3} VMAT2 inhibitors are agents that cause a depletion of neuroactive peptides (serotonin, norepinephrine and particularly dopamine) in nerve terminals and are used to treat conditions such as dyskinesias due to some antipsychotic medications.^{3,4} The reduction in these active neurotransmitters results in a decrease in choreic movements of the orofacial region, extremities, and torso, that are typical of patients with neurologic conditions such as tardive dyskinesia.⁴

The clinical development programme for deutetrabenazine for the treatment of tardive dyskinesia includes two phase III trials, NCT02195700 (ARM-TD) and NCT02291861 (AIM-TD), and a three-year open label extension study, NCT02198794 (RIM-TD).^{1,5,6} In the long-term extension study (NCT02198794), patients were administered deutetrabenazine orally twice daily at a dose of 12 mg/day, which was titrated based on dyskinesia control and tolerability up to a maximum total dose of 48 mg/day.¹

Key Innovation

In the UK, there are limited treatment options available for the management of tardive dyskinesia and no clear standard of care.⁷ Currently, there are also no National Institute for Health and Care Excellence (NICE) recommended treatment options for tardive dyskinesia. In addition, there is no clinical consensus on best supportive care or evidenced pharmacological treatment.^{7a} Deutetrabenazine contains deuterium, which replaces hydrogen at key positions within the tetrabenazine molecule. This substitution strengthens the carbon bonds, making them more difficult to cleave and prolonging the drug's plasma half-life, thus reducing fluctuations of medicine levels in the plasma without altering protein-binding interactions.⁸ Additionally, deuterium substitution slows substrate metabolism which can give several potential clinical advantages, including a reduced dose to achieve desired systemic exposures, reduced peak concentrations, and reduced impact of drug interactions along with unchanged binding properties.⁹ Therefore, deutetrabenazine can be administered at lower doses relative to other medicinal products used to treat movement disorders to achieve a comparable systemic exposure to the active α and β -HTBZ metabolites, resulting in a more favourable side effect profile.⁹

Regulatory & Development Status

Deutetrabenazine does not currently have Marketing Authorisation in the EU/UK for any indication.

Deutetrabenazine has the following regulatory designations/awards for tardive dyskinesia:^{10,11}

- Priority Review in the US in 2017 for the treatment of tardive dyskinesia
- Breakthrough Therapy Designation in the US in 2015 for the treatment of tardive dyskinesia

Patient Group

Disease Area and Clinical Need

^a Information provided by Teva Pharmaceuticals Ltd

Tardive dyskinesia is an involuntary neurological movement disorder caused by the use of dopamine receptor-blocking agents, such as antipsychotics, and antiemetics, which are prescribed to treat certain psychiatric or gastrointestinal conditions.^{4,12} The reasons why some people who take these medicines may get tardive dyskinesia, and some people do not, is unknown.¹² It typically manifests as a late and sometimes persistent complication of this therapy, and is characterised by involuntary stereotyped, choreic, athetoid, and/or dystonic movements in one or more areas of the body, including the orofacial region (e.g., tongue thrusting, lip smacking and/or pursing, grimacing), extremities (e.g., stereotypic piano-playing movements, flexion/extension of the ankles or toes), and torso (e.g., choreoathetoid movements, pelvic rocking).^{4,13} These symptoms can be particularly distressing, interfering with speech and eating.⁴ Other symptoms include jerky movements such as tapping or moving the hands and feet, slow movements such as writhing or squirming, and muscle spasms which cause posture change.¹⁴ Risk factors for tardive dyskinesia include long-term use of antipsychotic medicines, higher dosages, and older medications (first-generation antipsychotics). Additional risk factors include older age, previous extrapyramidal symptoms, among other intrinsic and extrinsic factors.¹⁵

The potential prevalence of tardive dyskinesia is difficult to accurately assess. It has been estimated in some studies to be as high as approximately 20% in patients chronically treated with antipsychotic medication, or 25.3% according to a global meta-analysis.^{16,17} In England 2023-24, there were 189 finished consultant episodes (FCE), and 113 admissions for drug-induced dystonia (ICD-10 code G24.0), which includes dyskinesias. This resulted in 804 FCE bed days and 7 day cases.¹⁸

Recommended Treatment Options

There are currently no NICE recommended treatments for tardive dyskinesia. In the UK, there are limited treatment options available for the management of tardive dyskinesia and no clear standard of care.⁷ One option is to withdraw or reduce the dose of the underlying antipsychotic treatment, but this may be inappropriate or destabilise the patients' psychiatric condition leading to increased healthcare resource utilisation.¹⁹⁻²¹

Clinical Trial Information

Trial	RIM-TD, NCT02198794, EudraCT 2014-001891-73; An Open-Label, Long-Term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia Phase III – completed Locations: 5 EU countries and the US Study completion date: December 2020
Trial Design	Randomised, quadruple masked, parallel assignment - open label 3-year extension study
Population	N=343 (actual); patients aged 18 years and older with moderate to severe tardive dyskinesia, who completed previous studies (NCT02195700 and NCT02291861). 337 patients were eligible for analysis.
Intervention(s)	Experimental Part A (screening period, titration period and long-term treatment period): Participants received deutetrabenazine orally twice daily starting at 12 mg/day. The dose was increased weekly in 6mg increments, based on dyskinesia control and tolerability up to a maximum total dose of 48 mg/day

	- Active comparator Part B: Participants received stable dose deutetrabenazine for 1 week in randomised withdrawal period and continued to receive this dose for an additional 12 weeks - Part C: EU participants who completed Part B continued treatment with deutetrabenazine at the same dose for 52 weeks
Comparator(s)	Matched placebo for 1 week in randomised withdrawal period and thereafter received deutetrabenazine (stable dose) for 12 weeks.
Outcome(s)	Primary outcome measures: - Part A, B and C: Number of participants with treatment-emergent adverse events (TEAEs), serious TEAEs, severe TEAEs, medicine-related TEAEs, and TEAEs leading to withdrawal [Time frame: Baseline up to the end of follow-up (4 weeks after the last dose of study medicine; mean exposure: up to approximately 866.1 days)] - Part B: Change from day 1 visit in total motor Abnormal Involuntary Movement Scale (AIMS) score at day 7 visit, as assessed by blinded central video rating [Time Frame: Day 1 of Part B, day 7 of Part B] See trial record for full list of other outcome measures.
Results (efficacy)	At Week 145 (mean dose: 39.4 ± 0.83 mg/day), mean $\pm$ standard error (SE) change from baseline in total motor AIMS score was -6.6 ± 0.37 and 67% of patients achieved $\geq 50\%$ improvement in total motor AIMS score. Based on Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC), 73% and 63% of patients achieved treatment success, respectively. Quality of life improvements were also observed. ²²
Results (safety)	Over a mean (SE) of 106.5 (3.20) weeks of treatment (up to 158 weeks for safety assessments) and 688 patient-years of exposure, deutetrabenazine was generally safe and well tolerated. The exposure-adjusted incidence rates (EAIR) for patients who experienced any adverse events (AE) was 1.24 patients per patient-year. The EAIRs for severe AEs, treatment-related AEs; serious AEs; and AEs leading to discontinuation, dose suspension, and dose reduction were generally low. EAIRs for AEs of interest, including depression, parkinsonism, and torsade de pointes/QT prolongation, were low. The most commonly reported AEs were anxiety, depression, somnolence, decreased weight, and urinary tract infection. In general, the incidence of these AEs was lower during the titration vs. the maintenance period, which is expected given the longer duration of the maintenance period. Exceptions with a numerically higher incidence during the titration vs. maintenance period included headache (4% vs. 3%) and fatigue (3% vs. 2%). The most common abnormal electrocardiogram findings were Fridericia's corrected QT interval (QTcF) >450 ms (30 [9%] patients) and change in QTcF >30 ms (45 [13%] patients). Eight deaths were reported during the study; none were considered to be related to study drug by the investigator. ²²

Clinical Trial Information

Trial	AIM-TD, NCT02291861, EudraCT 2014-003135-19; A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia Phase III – completed Locations: 5 EU countries and the US Study completion date: August 2016
Trial Design	Randomised, triple masked, parallel assignment
Population	N=298 (actual); patients aged 18 to 80 years with moderate to severe tardive dyskinesia
Intervention(s)	Deutetrabenazine tablets administered twice daily at a dose of either 12 mg/day, or 24 mg/day, or 36 mg/day
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: Change in total motor AIMS score from baseline to week 12 using a mixed model for repeated measures (MMRM) [Time frame: Day 0 (baseline), weeks 2, 4, 8 and 12] See trial record for full list of other outcomes.
Results (efficacy)	From baseline to week 12, the least-squares mean AIMS score improved by –3.3 points (SE 0.42) in the deutetrabenazine 36 mg/day group, –3.2 points (0.45) in the 24 mg/day group, and –2.1 points (0.42) in the 12 mg/day group, with a treatment difference of –1.9 points (SE 0.58, 95% CI –3.09 to –0.79; p=0.001), –1.8 points (0.60, –3.00 to –0.63; p=0.003), and –0.7 points (0.57, –1.84 to 0.42; p=0.217), respectively, versus –1.4 points (0.41) in the placebo group.²³
Results (safety)	The rate of AEs was similar between patients in the deutetrabenazine 36 mg/day group (n=38/74 [51%]), 24 mg/day group (n=32/73 [44%]), and 12 mg/day group (n=36/74 [49%]), and those in the placebo group (n=34/72 [47%]). SAEs were reported in four (5%) patients given deutetrabenazine 36 mg/day, six (8%) patients given 24 mg/day, and two (3%) patients given 12 mg/day, compared with four (6%) patients given placebo. Two (1%) patients in the safety population died, one each in the deutetrabenazine 24 mg/day and 36 mg/day groups; neither death was deemed related to study medicine by the investigator or sponsor.²³

Clinical Trial Information	
Trial	ARM-TD, NCT02195700, EudraCT 2014-001890-15; A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia Phase II/III – completed Locations: 3 EU countries and the US Study completion date: May 2015
Trial Design	Randomised, triple masked, parallel assignment

Population	N=117 (actual); patients aged 18 to 75 years with moderate to severe tardive dyskinesia
Intervention(s)	Deutetrabenazine tablets taken twice daily for 12 weeks
Comparator(s)	Placebo
Outcome(s)	Primary outcome measures: Change in centrally read AIMS score from baseline to week 12 using MMRM analysis [Time frame: Baseline (day 0), weeks 2, 4, 6, 9 and 12] See trial record for full list of other outcomes.
Results (efficacy)	Deutetrabenazine significantly reduced mean AIMS scores compared with placebo at week 12 (3.0 vs 1.6; P=.019). On the CGIC, 48.2% of deutetrabenazine patients experienced treatment success vs 40.4% for placebo (P=.40). In patients with central video AIMS ratings ≥ 6 at both screening and baseline (n=97), mean AIMS scores decreased by 3.5 in the deutetrabenazine group vs 1.8 for placebo (P=.017), and on the CGIC, treatment success was reported by 52.1% vs 34.7% of patients at Week 12 (P=.084). ²⁴
Results (safety)	Treatment-emergent AEs were reported in 70.7% and 61% of deutetrabenazine and placebo groups, respectively. The most common AEs reported were somnolence (n=8 [13.8%] vs n=6 [10.2%]) and headache (n=3 [6.9%] vs n=6 [10.2%]) in the deutetrabenazine and placebo groups, respectively. Both groups had low rates of psychiatric AEs, such as psychosis (n=1 [1.7%] deutetrabenazine vs n=0 placebo) and suicidal ideation (n=0 deutetrabenazine vs n=1 [1.7%] placebo). One (1.7%) deutetrabenazine patient withdrew due to AEs vs two (3.4%) in the placebo group. ²⁴

Estimated Cost

The cost of deutetrabenazine is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Ricciardi et al. Treatment Recommendations for Tardive Dyskinesia. 2019.²⁵
- Essex Partnership University NHS Foundation Trust. Formulary and Prescribing Guidelines - Section 9: Management of Movement Disorders and Extrapyrimal Side Effects. 2017.²⁶
- American Academy of Neurology (AAN). Evidence-based guideline: Treatment of tardive syndromes. 2013.²⁷

Additional Information

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